R E M A R K S

Information Disclosure Statements

1. On the copy of sheet 2 of the May 16, 2005 IDS Form returned with the previous Office Action of July 29, 2008, the Examiner drew a line through JP 2726672. However, JP 2726672 should have been considered and made of record, since it is a related family member of USP 4,952,581. The Examiner is therefore respectfully requested to return to the undersigned a copy of sheet 2 of the May 16, 2005 IDS Form, with the Examiner's initials next to each cited publication, including JP 2726672.

2. For the reasons set forth in applicants' INFORMATION DISCLOSURE STATEMENT filed June 29, 2010, the Examiner is respectfully requested to return to the undersigned a copy of the September 5, 2007 IDS Form with an indication thereon that the cited publication (which included an English-language abstract) was considered and made of record.

Presently Claimed Invention

Applicants' present claim 1 is directed to a therapeutic composition for treating glaucoma comprising a combination of pharmaceutically effective amounts of drugs comprising (i) a Rho

kinase inhibitor selected from the group consisting of (R)-trans-N-(pyridin-4-yl)-4-(1-aminoethyl)cyclohexane carboxamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide, 1-(5-isoquinolinesulfonyl)-homopiperazine and 1-(5-isoquinolinesulfonyl)-2-methylpiperazine, or a salt or an ester thereof and (ii) a prostaglandin selected from the group consisting of isopropyl unoprostone, latanoprost, travoprost and bimatoprost, or a salt or ester thereof, and optionally a pharmaceutically acceptable carrier.

Applicants' present claim 2 concerns a therapeutic composition for treating glaucoma which comprises a combination of pharmaceutically effective amounts of drugs comprising (i) a Rho kinase inhibitor selected from the group consisting of (R)-trans-N-(pyridin-4-yl)-4-(1-aminoethyl)cyclohexane carboxamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide, 1-(5-isoquinolinesulfonyl)-homopiperazine and 1-(5-isoquinolinesulfonyl)-2-methylpiperazine, or a salt or an ester thereof and a (ii) prostaglandin selected from the group consisting of isopropyl unoprostone, latanoprost, travoprost and bimatoprost, or a salt or an ester thereof, wherein the actions of the Rho kinase inhibitor and the prostaglandin are complemented and/or enhanced by each other, and optionally a

pharmaceutically acceptable carrier.

Rejection Under 35 USC 103

Claims 1, 2 and 21 were rejected under 35 USC 103 as being unpatentable over EP 286903 ("Bito") in view of USP 7,015,210 to Aiken, P. Vasantha Rao et al., *Modulation of Aqueous Humor Outflow Facility by the Rho Kinase-Specific Inhibitor Y-27632*, 42 INV. OPHTHALMOL. VIS. SCI., 1029 (April 2001) and USP 6,271,224 to Kapin et al. for the reasons set forth in item no. 1 on pages 2 to 3 of the September 14, 2010 Office Action.

It was admitted in the previous Office Actions of July 29, 2008 and January 12, 2009 that Bito, Aiken and Rao et al. describe different methods of treating glaucoma using prostaglandins or Rho inhibitors.

It was admitted in the January 5, 2010 Office Action that Bito (i) does not specifically recite any of applicants' claimed prostaglandins and (ii) does not specify Rho-kinase inhibitors as effective combined therapeutics.

Applicants' Rebuttal of the 35 USC 103 Rejection

Bito et al. relate to a method for treating ocular hypertension or glaucoma using a mixture of an adrenergic

blocking agent and a prostaglandin derivative. Bito et al. state that the adrenergic blocking agent needs to be shown not to block the ocular hypotensive effects of PGs (column 3, lines 8 to 13 of Bito et al.) when combining the agents.

The above description can be read as follows: "it needs to be shown that other agents do not block the ocular hypotensive effects of a prostaglandin derivative," when combining a prostaglandin derivative with other agents.

On the other hand, lines 5 to 7 of the abstract of the enclosed copy of Shin-ichi Sato et al., "Pharmacological Profile of Hydroxy Fasudil as a Selective Rho Kinase Inhibitor on Ischemic Brain Damage," Life Sciences, 69, (2001), 1441-1453 state that hydroxy fasudil, a selective Rho kinase inhibitor, relaxed the $PGF_{2\alpha}$-induced contraction in canine basilar or middle cerebral arterial strips, concentration-dependently. This means that the Rho kinase inhibitor inhibited the effect of the prostaglandin derivative. It is thus concluded that one of ordinary skill in the art would have considered that a Rho kinase inhibitor would inhibit the effect of a prostaglandin derivative, and that the combination of an Rho kinase inhibitor and a prostaglandin was not advantageous.

In view of the above, it is respectfully submitted that when considering Bito et al. in light of the technical knowledge at the time of applicants' invention, one of ordinary skill in the art would have been taught away from combining an Rho kinase inhibitor and a prostaglandin derivative.

Aiken is directed to a method for treating or preventing ophthalmic disorders by reducing intraocular pressure comprising the administration of one or more aldosterone receptor antagonists that contain a 9,11-epoxy moiety (see the Abstract of Aiken). As an optional further ingredient, Aiken mentions a prostaglandin (see claim 2 of Aiken).

It is evident that Bito et al. and Aiken are being relied upon only for their disclosures of prostaglandins.

Clearly, Bito et al. and Aiken considered that the administration of a prostaglandin by itself was insufficient to effectively reduce intraocular pressure, so both Bito et al. and Aiken employed other drugs, namely an andrenergic blocking agent in Bito et al., or an aldosterone receptor antagonist containing a 9,11-epoxy moiety in Aiken. These other drugs employed by Bito et al. and Aiken are not recited in applicants' claims. Bito et al. and Aiken do not teach or suggest a Rho inhibitor as recited in applicants' present claims.

Rao et al. is directed to a Rho kinase-specific inhibitor Y-27632 [(+)-R-trans-4-(1-aminoethyl)-N-(4-pyridyl)cyclohexano-carboxyamide]. Rao et al. do not teach or suggest combining such Rho kinase-specific inhibitor Y-27632 with a prostaglandin as recited in applicants' present claims.

Kapin et al. disclose a method of treating glaucoma by administering an isoquinolinesulfonyl compound (see the Abstract of Kapin et al.). Kapin et al. disclose the hydrochloride salt of 1-(5-isoquinolinesulfonyl)-homopiperazine ("fasudil"). Fasudil was discussed hereinabove. Kapin et al. do not teach or suggest the specific combination of drugs (such as a prostaglandin) as recited in applicants' present claims.

For the following reasons, based on the teachings of the references, it is respectfully submitted that one of ordinary skill in the art would not have arrived at the presently claimed invention.

(1) There is a potential difficulty when using plural drugs, namely, possible serious drug-drug interactions. The combining of drugs is thus vastly different than the combining of non-drug chemical compounds, for example, detergents.

(2) As discussed hereinabove, there was a disincentive in the art to combine a Rho kinase inhibitor and a prostaglandin

derivative at the time of the presently claimed invention. Accordingly, it is respectfully submitted that the Office Action did not set forth a *prima facie* case of obviousness.

Column 8, lines 31 to 32 of Bito et al. state that "the effects of these two drugs [timolol and a PEG] must be at least additive." Thus, column 8, lines 31 to 32 of Bito et al. describe only a mere additive effect of each drug.

Attention is directed to applicants' Figs. 2 to 4. Applicants' Fig. 1 shows a similar behavior as that of applicants' Fig. 2, and is considered to bring about the same result as that of Fig. 2 over time.

It is respectfully submitted that applicants' Figs. 2 to 4 (which were reproduced on pages 11 to 13 of applicants' RESPONSE UNDER 37 CFR 1.111 filed June 29, 2010) demonstrate that the intraocular pressure reducing effect 6 to 8 hours after administration of the respective agents in combination, as recited in applicants' present claims, show a synergistic effect.

It was alleged on page 3 of the September 14, 2010 Office Action that "applicants failed to compare the invention to the closest prior art." However, the "closest prior art" was not identified in said Office Action.

It was stated on page 3 of the September 14, 2010 Office Action that the data which applicants rely on involve comparisons to individual elements of the combination composition. However, each of the references teach only one element of applicants' combination. Applicants are not required to compare the results of their invention with the results of their invention. See MPEP 716.02(g)III), which is reproduced as follows:

> "Although evidence of unexpected results must compare the claimed invention with the closest prior art, applicant is not required to compare the claimed invention with subject matter that does not exist in the prior art. *In re Geiger*, 815 F.2d 686, 689, 2 USPQ2d 1276, 1279 (Fed. Cir. 1987) (Newman, J., concurring) (Evidence rebutted *prima facie* case by comparing claimed invention with the most relevant prior art. Note that the majority held the Office failed to establish a *prima facie* case of obviousness.); *In re Chapman*, 357 F.2d 418, 148 USPQ 711 (CCPA 1966) (Requiring applicant to compare claimed invention with polymer suggested by the combination of references relied upon in the rejection of the claimed invention under 35 U.S.C. 103 'would be requiring comparison of the results of the invention with the results of the invention.' 357 F.2d at 422, 148 USPQ at 714.)."

It was further asserted on page 3 of the Office Action that applicants tested only two of the four claimed prostaglandins. However, such two prostaglandins represent two prostaglandins disclosed in column 10, lines 42 to 56 in Aiken.

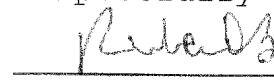
It was also contended on page 3 of the September 14, 2010 Office Action that applicants' data provided "less than an additive reduction of intraocular pressure." However, there is nothing in the Office Action which demonstrates how this allegation was arrived at.

Withdrawal of the 35 USC 103 rejection is respectfully requested.

Reconsideration and allowance of the above-identified application are respectfully requested.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted,



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Encs.: (1) PETITION FOR EXTENSION OF TIME

(2) copy of Life Sciences, 69, (2001), 1441-1453